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Salt intake, cured meat consumption, refrigerator use and stomach cancer incidence: a prospective cohort study[☆] (Netherlands)

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Abstract

Objective: Many case–control studies have reported that salt and cured meat intake are positively, and refrigerator use is inversely, associated with stomach cancer risk. In the current prospective study these associations were evaluated.
Methods: The Netherlands Cohort Study consisted of 120,852 men and women ages 55–69 years at baseline in 1986. Salt exposure was measured by calculating mean daily sodium intake (dietary salt) from 150 food items and by specific salt questions. After 6.3 years of follow-up, 282 incident stomach cancer cases were available for analyses. Case-cohort analyses were based on the 282 cases and 3123 subcohort members.
Results: In multivariate analyses adjusted for age, sex, smoking, education, stomach disorders, history of stomach cancer in the family, rate ratios (RR) for increasing quintiles of energy-adjusted intake of dietary salt were 1.00, 1.49, 1.03, 1.54 and 1.18, respectively (p trend = 0.43). An inverse association was found between stomach cancer and salt added at the hot meal (p trend = 0.04). For salt added to home-made soup, use of salt at the table, salt preference and duration of refrigerator use, no associations were observed. Positive associations were found for bacon (RR highest/lowest intake = 1.33; 95% CI = 1.03–1.71) and other sliced cold meat (RR highest/lowest intake = 1.29; 95% CI = 0.96–1.72), but not for smoked sausage, total cold meats, rashers/bacon, boiled ham and smoked beef/pork loin roll.
Separate analyses among subjects with self-reported stomach disorders revealed higher RR of stomach cancer for dietary salt and several types of cured meat.
Conclusion: The present findings suggest that intake of dietary salt and several types of cured meat were weakly positively associated with stomach cancer risk.

Abbreviations: CI – confidence interval; RR – rate ratio

Introduction

Salt has been traditionally used as a food preservative and to improve the taste of food. For decades, salt has been hypothesized to play a role in the aetiology of stomach cancer. Salt acts as an irritant that leads to mucosal damage in the stomach, excessive cell replication and it makes the mucosa cells more susceptible to carcinogens from foods [1]. Numerous epidemiological studies have investigated the association between stomach cancer risk and salt or sodium intake (*e.g.*, [2–4]), salted foods (*e.g.*, [5–7]), salt added during cooking or at table (*e.g.*, [8–10]) and preference of salty taste (*e.g.*, [11–13]). In many case–control studies a positive association

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was reported between an indicator of high salt intake and stomach cancer risk, but in nearly all cohort studies no association was observed [14].

Increased risks have also been found for a high consumption of meat products (*e.g.*, [15–17]). Meat products like bacon, sausage, ham, salami often contain, besides much salt, also nitrite, nitrosamines, and may contain polycyclic aromatic hydrocarbons (in smoked meats) or heterocyclic amines (in cooked foods) [17]. It is not clear whether excessive salt or the other compounds are responsible for an increased stomach cancer risk. Long-term use of a refrigerator has been hypothesized to decrease stomach cancer risk (*e.g.*, [9, 18, 19]). There is no direct relation with stomach cancer, but refrigerator use may reflect a change in dietary habits such as increased fruit and vegetable consumption and a decreased consumption of salted and smoked foods.

Evidence on salt and cured meat consumption has been mostly derived from case–control studies, where information bias may be present. We investigated in the Netherlands Cohort Study on diet and cancer the association between salt intake, several types of cured meat and use of refrigerator and stomach cancer risk after 6.3 years of follow-up.

Materials and methods

The Netherlands Cohort Study

The Netherlands Cohort Study started in September 1986 [20]. The cohort included 62,573 women and 58,279 men aged 55–69 years at the start of the study. The participants originated from 204 municipalities in the Netherlands. Data on dietary habits and other risk factors for cancer were collected by means of a self-administered questionnaire. For data analysis the case-cohort approach was used in which cases are derived from the entire cohort (providing numerator information for cancer incidence rates), while the person-years at risk of the entire cohort are estimated from a random subcohort sample of 3500 subjects (providing denominator information for the rates) [21]. In contrast to nested case–control sampling, this subcohort can be used for multiple disease endpoints. After the baseline measurement, the subcohort (1688 men, 1812 women) was randomly sampled from the cohort and was followed up for vital status information. No subcohort members were lost to follow-up. Follow-up for incident cancer has been established by record linkage with cancer registries and a pathology register [22]. The present analyses are restricted to cancer incidence in the first 6.3 years of follow-up from September 1986 until December 1992.

Exposure assessment

Habitual consumption of food and beverages during the year preceding the study was assessed using a 150-item semi-quantitative food frequency questionnaire [23]. Dietary sodium intake was calculated from the 150 food items using the computerized Dutch food composition table [24]. In this study, the variable dietary sodium intake represents sodium naturally present in foods together with sodium added in food processing by food manufacturers, but does not include salt added during preparation or before consumption. Dietary sodium intake was validated against nine dietary records [23]. The Spearman correlation coefficient was 0.64. Sodium is recalculated as salt (sodium-chloride) and denoted as dietary salt throughout this article. In the questionnaire several questions specifically focused on the use of table salt, salt added when preparing a hot meal or home-made soup, and salt preference. These latter questions were originally developed in relation to the food frequency questionnaire used by Willett in several cohort studies. In that setting, only acceptability was tested in a pilot study. The questions on salt preference of soup from a can or package and taste of food in restaurants were evaluated in two separate studies in which limited urine collections were available. The average salt excretion was assessed in a study among 75 women using one or two 24-h urine samples and in a study among 83 men using three consecutive samples of overnight (12-h) urine. Salt excretion was consistently lower in the groups of subjects who considered soup from a can or package or restaurant food too salty as compared with adequate, with the exception of women scoring the soup question. The associations for the restaurant question were statistically significant (unpublished data). Two questions concentrated on the use of a refrigerator and freezer (see Appendix A).

Foods that have a major contribution to the total salt intake are bread, cheese and cured meat. In the Netherlands, cured meat contains a mixture of salt, nitrate and nitrite, and was therefore interesting to study with regard to methods of food preparation. Participants were asked to report their frequency of consumption of six types of cured meat: bacon and smoked sausage eaten at the hot meal; boiled ham, rashers/bacon, smoked beef/pork loin roll and other sliced cold meat eaten at the cold meal. The seven answer categories ranged from 'never or less than once per month' to '6–7 times per week'. Participants had to indicate the

consumption amount in grams or household units (slices). In a validation study, the Spearman correlation coefficient between the questionnaire and a nine day diet record was 0.54 for meat products [23].

Data analysis

After excluding subjects reporting prevalent stomach cancer at baseline, cases with *in situ* stomach carcinoma, cases with stomach cancer other than carcinoma or without microscopically confirmed stomach cancer, 310 (242 men, 68 women) incident stomach carcinoma cases remained. In the subcohort, 1630 men and 1716 women remained after excluding prevalent cancer cases other than skin cancer. Furthermore, subjects with incomplete or inconsistent dietary data were also excluded [23], leaving 282 (219 men, 63 women) stomach cancer cases and 3123 subcohort members (1525 men, 1598 women) for the analyses.

Dietary salt intake was energy-adjusted by using the residual method in order to assess the independent contribution of salt [25]. Daily mean intake of cured meat (g/day) was calculated by multiplying frequency and consumption amount. The variables boiled ham, rashers/bacon, smoked beef/pork loin roll and other sliced cold meat were combined into the variable total sliced cold meats. The variables were categorized into quintiles (dietary salt intake) or categories (other salt variables, all cured meat variables and use of refrigerator and freezer) depending on the distribution in the subcohort. The answering categories 'often' and 'very often' from the table salt question and 'not salty enough' and 'far from salty enough' from the salt preference questions were combined due to few cases in the separate answer categories.

Intake of salt and cured meat differed between men and women. However, results of analyses by sex were very similar. Therefore, results were presented for men and women together. Mean daily intake of dietary salt, salt added to a hot meal or home-made soup, cured meat and mean years of refrigerator use were presented for all stomach cancer cases and subcohort members. Mean values of salt intake, salt added to the hot meal and home-made soup, total cured meat (a combination of all cured meat variables) and years of refrigerator use were compared across the various categories of the potential confounders. Variables that were considered as potential confounders were age (55–59, 60–64, 65–69 years), sex, level of education (low, medium and high) [26], self-reported stomach disorders (yes or no), family history of stomach cancer (yes or no), smoking status (never, ex-smoker and current smoker). In this study, stomach disorders were defined as having any stomach disease in the past that required medical attention (*e.g.*, peptic ulcer, gastritis).

Data were analysed using the case-cohort approach [21]. Rate ratios (RRs) of stomach cancer and their 95% confidence intervals (CI) were computed for the variables, using the GLIM statistical package [27]. Exponentially distributed survival times were assumed in the follow-up period. Specific macros were developed to account for the additional variance introduced by using the subcohort instead of using the entire cohort [28]. Tests for trend in the RRs were based on likelihood ratio tests and two-sided p-values were used throughout this article. Age- and sex-adjusted as well as multivariate analyses were done for all variables. The multivariate model included the above-mentioned potential confounders. For cured meat, also dietary salt intake was added in the multivariate model. Because in previous analyses no associations were observed between total energy intake, nitrate and nitrite intake [29] and stomach cancer risk, these factors were not considered as confounders.

To evaluate a potential influence of prediagnostic symptoms of stomach cancer on salt intake and cured meat consumption, we compared intake of cases diagnosed in the first two years of follow-up with later cases [30]. Furthermore, analyses for salt intake and cured meat were conducted for subjects with and without stomach disorders to evaluate whether results are different due to changes in dietary habits related to stomach disorders.

Results

Nearly all participants answered the question about use of table salt (99.1%), salt added to the hot meal (98.0%), use of refrigerator (96.6%) and freezer (97.7%). The questions about salt added to home-made soup, taste of soup from a pack or can or taste of restaurant food were answered by 86.5, 89.7 and 85.3% of the participants, respectively.

In Table 1 the mean intake of salt and cured meat in all stomach cancer cases and subcohort members is shown. The cases had a higher dietary salt intake and consumed more bacon (as component of the hot meal), total sliced cold meats, rashers/bacon and other sliced cold meat, but less smoked beef/pork loin roll than the subcohort members. There were no differences between the case group and subcohort members with respect to salt added to the hot meal or home-made soup and smoked sausage, nor for years of refrigerator use and percentage of freezer users. A higher percentage of the cases often used table salt compared to the subcohort

Table 1. Salt intake, consumption of cured meat, use of refrigerator and freezer, use of table salt, salt preference in all stomach cancer cases, case-group with first and second year cases excluded and subcohort members: Netherlands Cohort Study 1986–1992

Variables	Cases	Subcohort
	All n = 282	n = 3123
	Mean (SD[a])	Mean (SD[a])
Salt intake (g/day)		
Salt in foods (dietary salt)	6.4 (1.5)	5.8 (1.5)
Salt added to the hot meal during cooking[b]	4.0 (4.5)	4.0 (4.0)
Salt added to home-made soup during cooking[b]	0.6 (0.8)	0.6 (0.9)
Cured meat (g/day)		
Bacon as component of the hot meal	2.5 (4.2)	2.1 (3.7)
Smoked sausage as component of the hot meal	2.4 (2.3)	2.5 (2.6)
Total sliced cold meats	15.1 (17.3)	12.9 (15.0)
Boiled ham	4.5 (6.9)	4.4 (7.1)
Rashers, bacon	1.6 (4.1)	1.4 (4.0)
Smoked beef, pork loin roll	2.0 (4.3)	2.5 (5.5)
Other sliced cold meat	7.2 (12.5)	4.6 (8.5)
Use of refrigerator (years)	26.1 (7.9)	25.6 (7.6)
	n (%)	n (%)
Use of freezer[b]		
Yes	181 (64.2)	1952 (62.5)
No	97 (34.4)	1099 (35.2)
Use of slat at table[b]		
Never	113 (40.2)	1270 (40.7)
Seldom	87 (31.0)	875 (28.0)
Sometimes	55 (19.6)	746 (23.9)
Often/very often	26 (9.3)	204 (6.6)
Taste of soup from a pack or can[b]		
Not salty enough	7 (2.8)	74 (2.4)
Good	100 (39.5)	1211 (35.9)
A little too salty	74 (29.2)	935 (29.9)
Much too salty	70 (27.7)	673 (21.5)
Taste of restaurant food[b]		
Not salty enough	13 (5.5)	173 (5.5)
Good	153 (64.6)	1801 (57.7)
A little too salty	54 (22.8)	557 (17.8)
Much too salty	13 (5.5)	130 (4.2)

[a] Standard deviation.
[b] Because of missing values, the numbers do not add up to 282 cases and 3123 subcohort members.

members, but also indicated that the taste of soup from a pack or can or restaurant food was much too salty. Differences in salt and cured meat intake between early diagnosed cases and later cases were small and not statistically significant (data not shown).

There was no association between energy-adjusted dietary salt intake, salt added to home-made soup and age (Table 2). The amount of salt added to the hot meal and the consumption of total cured meat decreased with increasing age. Men had a higher intake of dietary salt, salt added to the hot meal and home-made soup and consumption of total cured meat compared to women. Current smokers used more salt when preparing the hot meal and consumed more total cured meat. Subjects in the lowest educational level added more salt to the hot meal and consumed more total cured meat. Subjects that reported to have stomach disorders consumed more cured meat than subjects without stomach disorders and subjects with a family history of stomach cancer consumed less cured meat than subjects without a family history of stomach cancer. There were no differences in years of refrigerator use between the categories of potential confounders, except that subjects of the lowest educational level reported to use the refrigerator less long than subjects of the higher educational levels.

Table 2. Mean intake (standard deviation (SD)) of dietary salt intake, salt added to the hot meal or to home-made soup, consumption of total cured meat and mean years (SD) of refrigerator use in the subcohort for several characteristics for men and women together: Netherlands Cohort Study 1986–1992

Characteristics	Dietary salt intake	Salt added to the hot meal during cooking	Salt added to home-made soup during cooking	Consumption of total cured meat	Refrigerator use
	g/day (SD)	g/day (SD)	g/day (SD)	g/day (SD)	years (SD)
Age (years)					
55–59	5.8 (1.5)	4.3 (4.1)	0.6 (0.8)	18.2 (16.7)	25.4 (7.2)
60–64	5.8 (1.5)	3.9 (3.9)	0.6 (1.1)	17.8 (16.2)	25.7 (7.6)
65–69	5.8 (1.5)	3.8 (3.9)	0.6 (0.8)	16.2 (16.2)	25.8 (8.2)
Sex					
Men	6.6 (1.5)	4.3 (4.3)	0.7 (1.1)	20.7 (18.8)	26.2 (7.4)
Women	5.3 (1.3)	3.7 (3.6)	0.5 (0.7)	14.5 (13.0)	25.1 (7.8)
Cigarette smoking status					
Never	5.6 (1.5)	3.7 (3.6)	0.6 (0.8)	15.2 (14.4)	24.6 (7.9)
Ex-smoker	6.1 (1.5)	3.7 (3.4)	0.5 (0.7)	17.3 (15.3)	26.3 (7.3)
Current smoker	6.1 (1.8)	4.7 (4.8)	0.6 (1.2)	20.2 (19.1)	26.0 (7.5)
Education level					
Primary school/lower vocational	6.1 (1.5)	4.3 (4.2)	0.7 (1.1)	18.5 (17.5)	24.5 (7.7)
Secondary school/medium	5.8 (1.5)	3.8 (3.9)	0.5 (0.7)	16.2 (14.9)	26.8 (7.7)
Vocational	5.8 (1.5)	3.6 (3.3)	0.5 (0.7)	17.0 (15.2)	27.1 (6.4)
University/higher vocational					
Stomach disorders					
No	5.8 (1.5)	4.0 (4.0)	0.6 (0.9)	17.4 (16.4)	25.6 (7.7)
Yes	6.1 (1.5)	4.1 (4.1)	0.6 (0.7)	18.6 (16.1)	25.5 (7.2)
Family history of stomach cancer					
No	5.8 (1.5)	4.0 (4.0)	0.6 (0.9)	17.6 (16.4)	25.6 (7.7)
Yes	6.1 (1.5)	4.1 (3.7)	0.5 (0.6)	16.0 (17.0)	25.7 (6.6)

Age- and sex-adjusted and multivariate adjusted RRs are presented in Table 3. Since the results were quite similar, these are described for multivariate analyses only. For dietary salt intake, the RRs were all higher than one, but without a linear trend. There was a significant inverse association between stomach cancer risk and salt added to the hot meal (trend $p = 0.04$). Salt added to home-made soup and use of table salt showed no clear association with stomach cancer risk. Subjects who indicated that the taste of soup or restaurant food was much too salty appear to have an increased stomach cancer risk, and subjects who indicated that the taste of restaurant food was not salty enough appear to have a decreased risk. Use of a refrigerator and freezer was not associated with stomach cancer risk. High consumption of bacon as component of the hot meal was associated with a significantly increased stomach cancer risk (RR highest *versus* lowest consumption category = 1.33, 95% CI = 1.03–1.71). No clear associations were observed between consumption of smoked sausage, total sliced cold meats, rashers/bacon, smoked beef/pork loin roll and stomach cancer. The RR of highest *versus* lowest category of boiled ham consumption was 0.77 (95% CI = 0.56–1.07) and for other sliced cold meat was 1.29 (95% CI = 0.96–1.72), but for both variables no significant trend in risk was observed. Additional adjustment for dietary salt intake in the model of the cured meat variables did not substantially change the risk estimates (data not shown). In an earlier analysis, total cured meat intake as source of nitrite was also not significantly associated with stomach cancer risk [29]. Exclusion of cases diagnosed in the first or second year of follow-up did not substantially change the results (data not shown).

Analyses among subjects with and without stomach disorders revealed different associations (Table 4). The RRs for dietary salt among subjects with stomach disorders were all higher than one, but there was no significant trend in risk (p-trend = 0.08). For salt added to home-made soup, a significant positive trend in risk was found (p-trend = 0.003) while an inverse trend in risk was found (p-trend = 0.04) for subjects without stomach disorders. RRs of bacon, smoked sausage, total sliced cold meats rashers/bacon and other sliced cold meat for people with stomach disorders were higher than one, although no RR was significantly increased. High consumption of boiled ham and smoked beef/pork in loin roll was not associated with an increased stomach

Table 3. RRs and 95% CI for stomach cancer according to salt intake, use of table salt, salt preference, use of refrigerator and freezer and consumption of cured meat: Netherlands Cohort Study 1986–1992

Exposure g/day (median intake)	Age and sex adjusted		Multivariate adjusted[a]
	Cases/person years in subcohort	RR (95% CI)	RR (95% CI)
Dietary salt (mean intake g/day)	47/3787	1.00	1.00
Quintile 1[b] (4.1)	68/3805	1.49 (1.02–2.19)	1.49 (1.00–2.23)
Quintile 2 (5.1)	47/3839	1.02 (0.68–1.55)	1.03 (0.67–1.59)
Quintile 3 (5.7)	67/3772	1.50 (1.02–2.19)	1.54 (1.03–2.30)
Quintile 4 (6.5)	53/3812	1.21 (0.81–1.81)	1.18 (0.77–1.80)
Quintile 5 (8.1)		*p*-trend 0.41	*p*-trend 0.43
Salt added to the hot meal during cooking (g/day)			
0[b]	41/2051	1.00	1.00
>0–2.5	84/5453	0.87 (0.59–1.29)	0.92 (0.61–1.38)
>2.5–5.0	65/5325	0.65 (0.43–0.97)	0.64 (0.42–0.98)
>5.0–10.0	64/4611	0.71 (0.47–1.06)	0.68 (0.44–1.04)
>10.0	20/1196	0.88 (0.50–1.54)	0.83 (0.46–1.50)
		p-trend 0.12	*p*-trend 0.04
Salt added to soup during cooking (g/day)			
0[b]	25/1538	1.00	1.00
>0–1.0	183/12124	0.98 (0.64–1.50)	0.92 (0.59–1.46)
>10.0	44/2794	0.91 (0.55–1.51)	0.85 (0.50–1.46)
		p-trend 0.68	*p*-trend 0.52
Use of salt at the table			
Never[b]	113/7714	1.00	1.00
Seldom	87/5344	1.04 (0.78–1.39)	1.05 (0.78–1.43)
Sometimes	55/3833	0.73 (0.52–1.01)	0.72 (0.51–1.02)
Often/very often	26/1254	1.00 (0.64–1.56)	0.90 (0.56–1.44)
		p-trend 0.23	*p*-trend 0.13
Taste of soup from a pack or can			
Not salty enough	7/459	1.10 (0.50–2.41)	1.06 (0.46–2.43)
Good[b]	100/6798	1.00	1.00
A little too salty	74/5758	0.94 (0.69–1.28)	0.98 (0.71–1.36)
Much too salty	70/4094	1.29 (0.94–1.77)	1.33 (0.95–1.86)
		p-trend 0.19	*p*-trend 0.12
Taste of restaurant food			
Not salty enough	13/1055	0.80 (0.63–1.01)	0.74 (0.40–1.36)
Good[b]	153/10981	1.00	1.00
A little too salty	54/3397	1.22 (1.08–1.38)	1.32 (0.94–1.85)
Much too salty	13/790	1.24 (0.98–1.57)	1.22 (0.65–2.28)
		p-trend 0.10	*p*-trend 0.05
Use of refrigerator			
1–<20 years[b]	48/3285	1.00	1.00
20–<40 years	191/13166	0.99 (0.71–1.37)	1.01 (0.71–1.42)
40 years and more	36/1905	1.10 (0.70–1.72)	1.11 (0.69–1.79)
		p-trend 0.72	*p*-trend 0.67
Use of freezer			
No[b]	181/11885	1.00	1.00
Yes	97/6693	0.91 (0.71–1.18)	0.95 (0.73–1.25)
Bacon as component of the hot meal			
0[b] (0.0)	131/10209	1.00	1.00
>0.0 (4.0)	151/8806	1.34 (1.05–1.70)	1.33 (1.03–1.71)
Smoked sausage as component of the hot meal			
0[b] (0.0)	74/4736	1.00	1.00
>0–3.0 (3.0)	133/9523	0.82 (0.61–1.10)	0.86 (0.63–1.17)
>3.0 (5.0)	75/4757	0.95 (0.68–1.07)	0.95 (0.67–1.35)
		p-trend 0.76	*p*-trend 0.77

Table 3. (Continued)

Exposure g/day (median intake)	Age and sex adjusted		Multivariate adjusted[a]
	Cases/person years in subcohort	RR (95% CI)	RR (95% CI)
Total sliced cold meats			
0[b] (0.0)	30/2527	1.00	1.00
>1.0–10.0 (5.0)	96/6994	1.17 (0.77–1.79)	1.18 (0.76–1.82)
>10.0–20.0 (14.0)	69/4967	1.08 (0.69–1.68)	1.06 (0.67–1.67)
>20.0 (30.0)	87/4526	1.38 (0.90–2.12)	1.33 (0.85–2.09)
		p-trend 0.16	*p*-trend 0.25
Boiled ham			
0[b] (0.0)	100/6037	1.00	1.00
>0–5.0 (3.0)	102/7623	0.75 (0.56–1.00)	0.78 (0.58–1.05)
>5.0 (12.0)	80/5355	0.79 (0.58–1.07)	0.77 (0.56–1.07)
		p-trend 0.11	*p*-trend 0.08
Rashers, bacon			
0[b] (0.0)	189/13307	1.00	1.00
>0.0 (2.0)	93/5709	0.97 (0.75–1.26)	0.94 (0.72–1.23)
Smoked beef, pork loin roll			
0[b] (0.0)	167/10480	1.00	1.00
>0.0 (2.0)	115/8535	0.92 (0.72–1.18)	0.92 (0.71–1.19)
Other sliced cold meat			
0[b] (0.0)	115/8918	1.00	1.00
>0–4.0 (2.0)	62/4417	1.04 (0.75–1.42)	1.07 (0.77–1.49)
>4.0 (11.0)	105/5680	1.29 (0.98–1.70)	1.29 (0.96–1.72)
		p-trend 0.07	*p*-trend 0.07

[a] RRs adjusted for age, sex, smoking status, level of education, stomach disorders and stomach cancer in the family.
[b] Reference category.

cancer risk in either subjects with or without stomach disorders.

Discussion

In this prospective cohort study, energy-adjusted intake of dietary salt was associated with an increased stomach cancer risk, but there was no clear trend with increasing risk. Salt added to food during cooking was inversely associated with risk. There was no association between salt added to home-made soup or use of table salt and stomach cancer risk. Results regarding salt preference questions were contrary to expectations. High intake of bacon and other sliced cold meat was associated with increased risks and high intake of boiled ham was associated with a decreased risk. There was no evidence that duration of refrigerator use or use of a freezer was related to stomach cancer in this study population.

Before interpreting the results of this study, several features of this cohort study should be discussed. This is a large population-based prospective cohort study with a relatively large number of cases (n = 310) after 6.3 years of follow-up. Selection bias due to loss-to follow-up is unlikely given the high completeness of follow-up of the cases and the subcohort person-years. It was possible to correct for several potential confounders because information about these factors was assessed in the questionnaire. However, the associations may still be confounded by unknown and unmeasured factors. Information bias due to random misclassification may have resulted in bias towards the null value. We tried, however, to prevent substantial misclassification of exposure by excluding subjects with incomplete and inconsistent data [23].

It is rather difficult to quantify salt intake. In the present study, salt intake was measured by calculating mean daily sodium intake from the 150-item semi-quantitative food frequency questionnaire. Furthermore, specific questions focused on salt added during cooking and at table and salt preference. Sodium intake was validated and the Spearman correlation coefficient was 0.64 [23], which suggests that the questionnaire is able to rank subjects reasonably well according to sodium intake. This sodium variable (sodium naturally

Table 4. RRs and 95% CI for stomach cancer according to salt intake and consumption of cured for stomach cancer cases with and without stomach disorders: Netherlands Cohort Study 1986–1992

Exposure	Subjects without stomach disorders		Subjects with stomach disorders	
	Cases/person years in subcohort	RR (95% CI)[a]	Cases/person years in subcohort	RR (95%CI)[a]
Dietary salt				
Quintile 1[b]	39/3408	1.00	8/347	1.00
Quintile 2	56/3352	1.50 (0.98–2.30)	11/415	1.27 (0.46–3.49)
Quintile 3	36/3481	0.92 (0.58–1.47)	11/352	1.34 (0.47–3.80)
Quintile 4	58/3446	1.52 (1.00–2.32)	9/297	1.45 (0.50–4.22)
Quintile 5	39/3465	0.99 (0.63–1.57)	14/322	2.17 (0.81–5.80)
		p-trend 1.00		*p*-trend 0.08
Salt added to the hot meal during cooking (g/day)				
0[b]	33/1861	1.00	8/181	1.00
>0–2.5	66/5014	0.89 (0.57–1.37)	18/402	1.02 (0.38–2.79)
>2.5–5.0	52/4656	0.68 (0.43–1.08)	12/632	0.45 (0.16–1.28)
>5.0–10.0	53/4169	0.70 (0.45–1.11)	11/404	0.60 (0.21–1.72)
>10.0	16/1093	0.82 (0.44–1.52)	4/103	0.87 (0.21–3.59)
		p-trend 0.12		*p*-trend 0.17
Salt added to soup during cooking (g/day)				
0	22/1388	1.00	3/131	1.00
> 0–1.0	153/10950	0.90 (0.57–1.44)	29/1102	1.13 (0.31–4.08)
> 1.0	28/2530	0.59 (0.33–1.05)	16/252	3.29 (0.85–12.69)
		p-trend 0.04		*p*-trend 0.003
Bacon as component of the hot meal				
0[b]	105/9120	1.00	25/1013	1.00
>0.0	123/8033	1.24 (0.95–1.63)	28/720	1.78 (0.97–3.25)
Smoked sausage as component of the hot meal				
0[b]	60/4203	1.00	13/501	1.00
>0–3.0	107/8621	0.82 (0.59–1.14)	26/830	1.08 (0.51–2.28)
>3.0	61/4329	0.88 (0.61–1.28)	14/402	1.30 (0.56–3.05)
		p-trend 0.51		*p*-trend 0.50
Total sliced cold meats				
0–10.0[b]	108/8744	1.00	18/728	1.00
>10.0–20.0	57/4417	0.96 (0.69–1.34)	11/497	0.91 (0.39–2.11)
>20.0	63/3993	1.03 (0.74–1.43)	24/508	1.93 (0.95–3.89)
		p-trend 0.89		*p*-trend 0.04
Boiled ham				
0[b]	82/5469	1.00	18/531	1.00
>0–5.0	88/6994	0.80 (0.59–1.10)	14/598	0.69 (0.32–1.49)
>5.0	58/4691	0.74 (0.52–1.05)	21/605	0.90 (0.44–1.81)
		p-trend 0.07		*p*-trend 0.79
Rashers, bacon				
0[b]	157/12054	1.00	32/1142	1.00
>0.0	71/5099	0.86 (0.64–1.15)	21/591	1.34 (0.73–2.48)
Smoked beef, pork loin roll				
0[b]	136/9529	1.00	30/879	1.00
>0.0	92/7624	0.96 (0.73–1.26)	23/854	0.84 (0.46–1.54)
Other sliced cold meat				
0[b]	93/8055	1.00	21/806	1.00
>0–4.0	52/4006	1.14 (0.80–1.62)	10/386	0.83 (0.36–1.92)
>4.0	83/5092	1.25 (0.92–1.71)	22/541	1.39 (0.70–2.76)
		p-trend 0.14		*p*-trend 0.31

[a] RRs adjusted for age, sex, smoking status, level of education, stomach disorders and stomach cancer in the family.
[b] Reference category.

present in foods and sodium added in food processing) is estimated to represent two-thirds of the sodium ingested [31]. For only some of the specific salt preference questions there was some evaluation of their informativeness; it remains to be seen how valid these questions overall are.

We did not estimate the total salt intake by combining the information on dietary salt intake and salt added during cooking and at the table because we could not account for salt loss during cooking and we had no information about the amount of salt added at the table. Nevertheless, when we added up dietary salt intake and salt added to the hot meal and home-made soup, the salt intake in the subcohort was 10.4 g/day. This corresponded relatively well with the estimated daily salt intake by adults in the Netherlands (9 g) [32] and the average daily salt intake reported in other European countries, which varied from 7.6 to 11.4 g [3, 31].

Overall, in the majority of case–control studies, positive associations were observed for (total) salt or sodium intake [2, 3, 33, 34], consumption of salted fish, salted meat, pickles and soup [5, 7, 16, 34–40], adding salt to food at dinner [5, 9, 41], preference of salty foods [4, 5, 11, 40, 42]. The relative risks reported ranged from 1.5 to 6.7 for various measures of salt intake [14]. In several other case–control studies no association was reported for (total) salt or sodium intake [43–45], salted foods [11, 13, 43, 46], for use of table salt [10, 47] or salt added to food [8, 13, 15, 16, 47], preference of foods with a salty taste [8, 12, 13, 15].

The few cohort studies that reported results on salt and stomach cancer risk found no clear associations [48–53]. Contrary to our finding that dietary salt intake was associated with an increased stomach cancer risk, the only cohort study that reported on sodium intake found no difference in mean daily sodium intake between cases and non-cases [48]. Two cohort studies reported a significantly increased risk for consumption of broiled fish (RR = 1.7) [52] and salted fish (RR = 2.0) [50]. The other three cohort studies found no association between stomach cancer incidence and the individual or total intake of several types of high-salted foods [49, 51, 53]. It is possible that the increased risks could be attributed to other compounds of the foods (possible carcinogens) developed during the preservation process, but not to salt content of the foods [7]. As in our study, use of table salt was not associated with stomach cancer risk in the only cohort study that reported on this association [49].

Most case–control studies have reported positive associations between meat products and stomach cancer risk [5, 7, 10, 15–17, 42, 47, 54, 55], but not all [9, 13, 33, 56]. A cohort study among Hawaiians of Japanese descent reported a non-significant positive association between stomach cancer risk and the consumption of processed meats [48, 49]. In an American study, only a positive association was found for bacon [50], and in a third study with subjects of Japanese ancestry no association was found for processed meat [53].

In our study, high consumption of bacon and other sliced cold meat were positively associated with stomach cancer risk, but this did not seem to be related with a high salt or nitrite content of these products. Earlier analyses indicated that nitrite was not clearly related with stomach cancer risk [29]. Additional adjustment for intake of salt or nitrite did not change the risk estimates. However, it is difficult to differentiate individual effects of salt and nitrite because of a high correlation between salt and total cured meat ($r = 0.47$), and nitrite and total cured meat ($r = 0.91$).

Duration of refrigerator use or freezer use was not associated with stomach cancer risk in the Netherlands Cohort Study, in contrast with the results of case–control studies performed in Europe or the USA, which rather consistently reported a decreased stomach cancer risk with long-term use of a refrigerator [2, 5, 9, 16, 18, 38, 54]. Three of the case–control studies did not find an association [15, 44, 47] and no other cohort study reported on this association.

In the Netherlands, the electric refrigerator was introduced in the household in the 1950s and after a period of 30 years, nearly all (98%) of households had a refrigerator [57]. Nearly 70% of cohort members reported to have had a refrigerator for 20–35 years at the start of the study. Therefore, the contrast in exposure is small and may be a reason for not finding an association. Moreover, refrigerator use is probably a rough indicator in this study population for storing conditions, certain food habits regarding preservation and preparation or availability of fresh food. In the Netherlands, almost everyone has had easy access to shops or supermarkets with fresh, well stored and preserved foods. It is possible that access to a refrigerator early in life is more important in relation to stomach cancer development. However, given the introduction of the electric refrigerator in the 1950s in the Netherlands, we were not able to study this in the Netherlands Cohort Study.

Subgroup analyses on stomach cancer risk and intake of salt and cured meat among subjects with and without stomach disorders revealed stronger associations in subjects with stomach disorders. These people consumed more cured meat compared to people without stomach disorders, but it is not clear whether this is a result of stomach disorders symptoms. We did not

observe a lower consumption of hot meal components and a higher consumption of cold meal components in people with stomach disorders like we found for people with possible preclinical symptoms of stomach cancer. An explanation for finding increased risks may be that subjects with stomach disorders (peptic ulcer or gastritis) may have an impaired mucosal barrier caused by a high salt diet which may lead to an easy penetration of carcinogens, *i.e.* nitrosamines present in foods or formed out of nitrite in cured meat. This seems to support the hypothesis that salt and nitrite are involved in an early stage of gastric carcinogenesis [1, 58].

An interesting finding is the interaction between salt and H. Pylori infection [59]. The mucosal cell proliferation in the antrum was positively correlated with salt intake in H. Pylori positive patients, while in patients without H. Pylori no relationship was found [59]. A part of the subjects with stomach disorders may be infected with H. Pylori. This finding suggests that it is important to have information on the percentage of infected people in the study population and that different results on salt and stomach cancer risk may be explained by different infection rates. In this respect, it is also possible that refrigeration was more relevant when H. Pylori infection was more prevalent in the Netherlands. Unfortunately, we did not have information on H. Pylori infection in the Netherlands Cohort Study. In summary, our data suggest that salt naturally present in foods and salt added in food processing is associated with a non-significantly increased risk for stomach cancer. No clear associations are found for other indicators of salt intake.

Analyses of cured meat variables showed that bacon and other sliced cold meat are positively associated with stomach cancer risk, although this probably cannot be explained by the salt or nitrite content of these products. There was no association between duration of refrigerator use and stomach cancer.

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Appendix A

Questions about salt added when preparing a hot meal or home-made soup, the use of table salt, salt preference, and the use of a refgerator and freezer from the baseline questionnaire; Netherlands Cohort Study 1986–1992.

Do you add salt during the preparation of the following dishes? If so, can you indicate how much salt is being added? (one tablespoon of salt = about seven teaspoons of salt)

. potatoes, pasta, rice *etc.*	☐ no	☐ yes	**if so, how much?**	... teaspoons per person
. vegetables	☐ no	☐ yes	**if so, how much?**	... teaspoons per person
. meat or fish	☐ no	☐ yes	**if so, how much?**	... teaspoons per person

When you are at dinner, do you thén add salt to your food?

☐ never ☐ seldom ☐ sometimes ☐ often ☐ very often

How often do you eat home-made soup? ... times per month. How many plates do you take?... plates each time. When you prepare this soup, for how many plates is this usually? ... plates

How much of the following ingredients do you usually use to make the soup taste good?

☐ stock cubes ... pieces	☐ dehydrated soup ... packs	☐ salt ... teaspoons	☐ only herbs
☐ maggi cubes ... pieces	☐ mixsoup ... boxes	☐ maggi ... drops	

Appendix A. (*Continued*)

How do you think soup from a pack or can usually tastes? ☐ far from salty enough ☐ not salty enough ☐ good ☐ a little too salty ☐ much too salty How do you think food in most of the restaurants and cafeterias usually tastes? ☐ far from salty enough ☐ not salty enough ☐ good ☐ a little too salty ☐ much too salty

Since when do you use a refrigerator? Since 19… Do you use a freezer? ☐ no ☐ yes

References

1. Correa P (1992) Human gastric carcinogenesis: a multistep and multifactorial process – First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* **52**: 6735–6740.
2. Graham S, Haughey B, Marshall J, *et al*. (1990) Diet in the epidemiology of gastric cancer. *Nutr Cancer* **13**: 19–34.
3. Nazario CM, Szklo M, Diamond E, et al. (1993) Salt and gastric cancer: a case–control study in Puerto Rico. *Int J Epidemiol* **22**: 790–797.
4. La Vecchia C, Negri E, Franceschi S, Decarli A (1997) Case–control study on influence of methionine, nitrite, and salt on gastric carcinogenesis in northern Italy. *Nutr Cancer* **27**: 65–68.
5. Buiatti E, Palli D, Decarli A, *et al*. (1989) A Case–control study of gastric cancer and diet in Italy. *Int J Cancer* **44**: 611–616.
6. Ramon JM, Serra ML, Cerdo C, Oromi J (1993) Nutrient intake and gastric cancer risk: a case–control study in Spain. *Int J Epidemiol* **22**: 983–988.
7. Ward MH, Lopez Carrillo L (1999) Dietary factors and the risk of gastric cancer in Mexico City. *Am J Epidemiol* **149**: 925–932.
8. Tuyns AJ (1983) Sodium chloride and cancer of the digestive tract. *Nutr Cancer* **4**: 198–205.
9. Coggon D, Barker DJ, Cole RB, Nelson M (1989) Stomach cancer and food storage. *J Natl Cancer Inst* **81**: 1178–1182.
10. Wu-Williams AH, Yu MC, Mack TM (1990) Life-style, workplace, and stomach cancer by subsite in young men of Los Angeles County. *Cancer Res* **50**: 2569–2576.
11. You WC, Blot WJ, Chang YS, *et al*. (1988) Diet and high risk of stomach cancer in Shandong, China. *Cancer Res* **48**: 3518–3523.
12. Negri E, La VC, D'Avanzo B, Gentile A, Boyle P, Franceschi S (1990) Salt preference and the risk of gastrointestinal cancers. *Nutr Cancer* **14**: 227–232.
13. Hansson LE, Nyren O, Bergstrom R, *et al*. (1993) Diet and risk of gastric cancer. A population-based case–control study in Sweden. *Int J Cancer* **55**: 181–189.
14. Kono S, Hirohata T (1996) Nutrition and stomach cancer. *Cancer Causes Control* **7**: 41–55.
15. Gonzalez CA, Sanz JM, Marcos G, *et al*. (1991) Dietary factors and stomach cancer in Spain: a multi-center case–control study. *Int J Cancer* **49**: 513–519.
16. Boeing H, Frentzel BR, Berger M, *et al*. (1991) Case–control study on stomach cancer in Germany. *Int J Cancer* **47**: 858–864.
17. Ward MH, Sinha R, Heineman EF, *et al*. (1997) Risk of adenocarcinoma of the stomach and esophagus with meat cooking method and doneness preference. *Int J Cancer* **71**: 14–19.
18. La Vecchia C, Negri E, D'Avanzo B, Franceschi S (1990) Electric refrigerator use and gastric cancer risk. *Br J Cancer* **62**: 136–137.
19. Boeing H, Frentzel BR (1991) Regional risk factors for stomach cancer in the FRG. *Environ Health Perspect* **94**: 83–89.
20. van den Brandt PA, Goldbohm RA, van't Veer P, Volovics A, Hermus RJ, Sturmans F (1990) A large-scale prospective cohort study on diet and cancer in The Netherlands. *J Clin Epidemiol* **43**: 285–295.
21. Self SG, Prentice RL (1988) Asymptotic distribution theory and efficiency results for case–cohort studies. *Ann Stat* **16**: 64–81.
22. van den Brandt PA, Schouten LJ, Goldbohm RA, Dorant E, Hunen PM (1990) Development of a record linkage protocol for use in the Dutch Cancer Registry for Epidemiological Research. *Int J Epidemiol* **19**: 553–558.
23. Goldbohm RA, van den Brandt PA, Brants HA, *et al*. (1994) Validation of a dietary questionnaire used in a large-scale prospective cohort study on diet and cancer. *Eur J Clin Nutr* **48**: 253–265.
24. Nevo tabel (1986) Dutch Food Composition table 1986–1987; *Nederlands voedingsstoffenbestand* 1986–1987. The Hague: Voorlichtingsbureau voor de Voeding.
25. Willett W, Stampfer MJ (1986) Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* **124**: 17–27.
26. van Loon AJM, Goldbohm RA, van den Brandt PA (1998) Socioeconomic status and stomach cancer incidence in men: results from the Netherlands Cohort Study. *J Epidemiol Commun Health* **52**: 166–171.
27. Baker R (1985) *Glim 3.77 Reference manual*. Oxford: Numerical Algorithms Group.
28. Volovics A, van den Brandt PA (1997) Methods for the analyses of case–cohort studies. *Biom J* **39**: 195–214.
29. van Loon AJM, Botterweck AAM, Goldbohm RA, Brants HAM, van Klaveren JD, van den Brandt PA (1998) Intake of nitrate and nitrite and the risk of gastric cancer: a prospective cohort study. *Br J Cancer* **78**: 129–135.
30. Botterweck AAM, van den Brandt PA, Goldbohm RA (1998) A prospective cohort study on vegetable and fruit consumption and stomach cancer risk in the Netherlands. *Am J Epidemiol* **148**: 842–853.
31. Hanneman RL, Moinier B (1988) Dietary salt intake and epidemiological studies. *Gut* **29**: 407–411.
32. Commissie Vermindering Gebruik Keukenzout (1986) *Vermindering gebruik keukenzout: Eindadvies*. Den Haag: Voedingsraad.

33. La Vecchia C, Negri E, Decarli A, D'Avanzo B, Franceschi S (1987) A case–control study of diet and gastric cancer in northern Italy. *Int J Cancer* **40**: 484–489.
34. Ramon JM, Serra L, Cerdo C, Oromi J (1993) Dietary factors and gastric cancer risk. A case–control study in Spain. *Cancer* **71**: 1731–1735.
35. Haenszel W, Kurihara M, Segi M, Lee RK (1972) Stomach cancer among Japanese in Hawaii. *J Natl Cancer Inst* **49**: 969–988.
36. Bjelke E (1974) Epidemiologic studies of cancer of the stomach, colon, and rectum; with special emphasis on the role of diet. *Scand J Gastroenterol Suppl* **31**: 1–235.
37. Kono S, Ikeda M, Tokudome S, Kuratsune M (1988) A case–control study of gastric cancer and diet in northern Kyushu, Japan. *Jpn J Cancer Res* **79**: 1067–1074.
38. Demirer T, Icli F, Uzunalimoglu O, Kucuk O (1990) Diet and stomach cancer incidence. A case–control study in Turkey. *Cancer* **65**: 2344–2348.
39. Palli D, Bianchi S, Decarli A, *et al.* (1992) A case–control study of cancers of the gastric cardia in Italy. *Br J Cancer* **65**: 263–266.
40. Lee JK, Park BJ, Yoo KY, Ahn YO (1995) Dietary factors and stomach cancer: a case–control study in Korea. *Int J Epidemiol* **24**: 33–41.
41. Tuyns AJ (1988) Salt and gastrointestinal cancer. *Nutr Cancer* **11**: 229–232.
42. Hoshiyama Y, Sasaba T (1992) A case–control study of stomach cancer and its relation to diet, cigarettes, and alcohol consumption in Saitama Prefecture, Japan. *Cancer Causes Control* **3**: 441–448.
43. Hu JF, Zhang SF, Jia EM, *et al.* (1988) Diet and cancer of the stomach: a case–control study in China. *Int J Cancer* **41**: 331–335.
44. Jedrychowski W, Boeing H, Popiela T, Wahrendorf J, Tobiasz AB, Kulig J (1992) Dietary practices in households as risk factors for stomach cancer: a familial study in Poland. *Eur J Cancer Prev* **1**: 297–304.
45. Harrison LE, Zhang ZF, Karpeh MS, Sun M, Kurtz RC (1997) The role of dietary factors in the intestinal and diffuse histologic subtypes of gastric adenocarcinoma: a case–control study in the US. *Cancer* **80**: 1021–1028.
46. Acheson ED, Doll R (1964) Dietary factors in carcinoma of the stomach: a study of 110 cases and 200 controls. *Gut* **5**: 126–131.
47. Correa P, Fontham E, Pickle LW, Chen V, Lin YP, Haenszel W (1985) Dietary determinants of gastric cancer in south Louisiana inhabitants. *J Natl Cancer Inst* **75**: 645–654.
48. Chyou PH, Nomura AM, Hankin JH, Stemmermann GN (1990) A case–cohort study of diet and stomach cancer. *Cancer Res* **50**: 7501–7504.
49. Nomura A, Grove JS, Stemmermann GN, Severson RK (1990) A prospective study of stomach cancer and its relation to diet, cigarettes, and alcohol consumption. *Cancer Res* **50**: 627–631.
50. Kneller RW, McLaughlin JK, Bjelke E, *et al.* (1991) A cohort study of stomach cancer in a high-risk American population. *Cancer* **68**: 672–678.
51. Kato I, Tominaga S, Matsumoto K (1992) A prospective study of stomach cancer among a rural Japanese population: a 6-year survey. *Jpn J Cancer Res* **83**: 568–575.
52. Ikeda M, Yoshimoto K, Yoshimura T, Kono S, Kato H, Kuratsune M (1983) A cohort study on the possible association between broiled fish intake and cancer. *Gann* **74**: 640–648.
53. Galanis DJ, Kolonel LN, Lee J, Nomura A (1998) Intakes of selected foods and beverages and the incidence of gastric cancer among the Japanese residents of Hawaii: a prospective study. *Int J Epidemiol* **27**: 173–180.
54. Risch HA, Jain M, Choi NW, *et al.* (1985) Dietary factors and the incidence of cancer of the stomach. *Am J Epidemiol* **122**: 947–959.
55. Sanchez-Diez A, Hernandez MR, Cueto EA (1992) Study of the relation between diet and gastric cancer in a rural area of the Province of Leon, Spain. *Eur J Epidemiol* **8**: 233–237.
56. Tuyns AJ, Kaaks R, Haelterman M, Riboli E (1992) Diet and gastric cancer. A case–control study in Belgium. *Int J Cancer* **51**: 1–6.
57. Berkel J, Tytgat GN (1982) Epidemiologie van het maagcarcinoom. *Ned Tijdschr Geneeskd* **126**: 1164–1172.
58. Correa P, Haenszel W, Cuello C, Tannenbaum S, Archer M (1975) A model for gastric cancer epidemiology. *Lancet* **2**: 58–60.
59. De Koster E, Buset M, Fernandes E, Deltenre M (1994) Helicobacter Pylori: the link with gastric cancer. *Eur J Cancer Prev* **3**: 247–257.